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EP-A- 0 132 375
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JOURNAL OF MEDICINAL CHEMISTRY, vol. 29, no. 9, September 1986, pages 1696-1702, American Chemical Society; J.E. ARROWSMITH et al.: "Long-acting dihydropyridine calcium antagonists. 1. 2-Alkoxymethyl derivatives incorporating basic substitu nts' Progr. Pharmacol. 5, 25 (1982)

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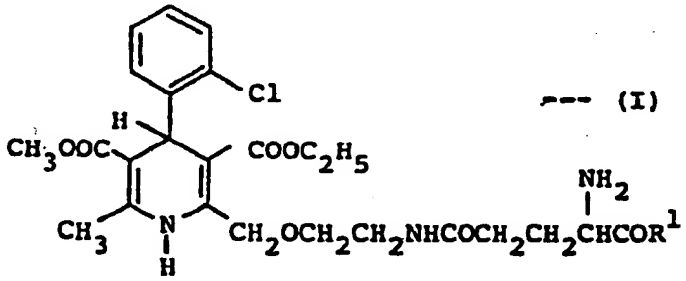
Description

This invention relates to certain dihydropyridines which are pro-drugs of the calcium antagonist amlodipine, which is chemically known as 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (see EP-B-0089167), and to intermediates useful in the preparation of these pro-drugs.

Calcium antagonists reduce the movement of calcium into the cell and are thus able to delay or prevent the cardiac contracture which is believed to be caused by an accumulation of intracellular calcium under ischaemic conditions. Excessive calcium influx during ischaemia can have a number of additional adverse effects which would further compromise the ischaemic myocardium. These include less efficient use of oxygen for ATP production, activation of mitochondrial fatty acid oxidation and, possibly, promotion of cell necrosis. Thus calcium antagonists are useful in the treatment or prevention of a variety of cardiac conditions, such as angina pectoris, cardiac arrythmias, heart attacks and cardiac hypertrophy. Calcium antagonists also have vasodilator activity since they can inhibit calcium influx in cells of vascular tissue and are thus also useful as antihypertensive agents and for the treatment of coronary vasospasm.

"Our European Patent Applications EP-A-0089167, EP-A-0119050, EP-A-0060674 and EP-A-00132375 and the reference J. Med. Chem., 29, 1696-1702 (1986) disclose certain 4-aryl-1,4-dihydropyridine derivatives having clacium antagonist activity. In addition Progr. Pharmacol., 5(1), 25-52 (1982) discusses structure-activity relationships of specific calcium antagonists."

Thus the invention provides 1,4-dihydropyridine derivatives of the formula (I) :



(I)

and their pharmaceutically acceptable salts, wherein R^1 is —OR^2 or —NH_2 in which R^2 is H, C_1-C_6 alkyl, phenyl or benzyl, the phenyl and benzyl groups being optionally substituted on the aromatic ring by one or two substituents each independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy and halo.

"Halo" means F, Cl, Br or I. C_2-C_6 alkyl and C_3-C_4 alkoxy groups can be straight or branched chain. The phenyl and benzyl groups are preferably unsubstituted. R^1 is preferably hydroxy.

The compounds of the formula (I) are useful for the treatment of various cardiovascular disorders, for example, hypertension and angina. The compounds of the formula (I) also display natriuretic activity and can improve renal function.

The compounds of formula (I) are metabolised to amlodipine and therefore display calcium antagonist activity in vivo after oral or parental administration. For example, following intravenous administration to dogs, these compounds lower coronary and systemic vascular resistance and are thus useful for the treatment of angina and hypertension. In addition, at least when the compounds of the formula (I) are administered parenterally, a pronounced natriuretic effect is also observed, which is believed to be due to preferential conversion of these pro-drugs to amlodipine in the kidney. These compounds are therefore useful (at least when given parenterally) in the treatment of patients with renal impairment, acute renal failure and in pre-operative care prior to surgery.

For human use, the compounds of the formula (I) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally or sublingually in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intravenously, intramuscularly or subcutaneously, or adminstered via a transdermal device.

For administration to man in the curative or prophylactic treatment of cardiac conditions and hypertension, oral dosages of the compounds will generally be in the range of from 2-200 mg daily for an average adult patient

(70 kg). Thus for a typical adult patient, individual tablets or capsules may contain from 1 to 100 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier. Dosages for parenteral administration would typically be within the range 1 to 10 mg per single dose as required.

In practice the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

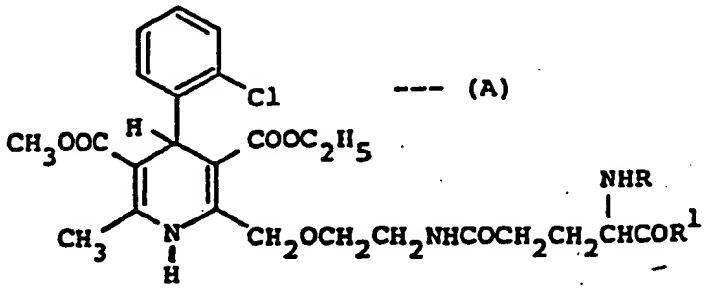
For parenteral administration, the compounds are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

The invention thus includes pharmaceutical compositions comprising a compound of the formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

The invention further provides a compound of the formula (I), or a pharmaceutically acceptable salt thereof, for use as a medicament.

The invention yet further provides the use of a compound of the formual (I), or of a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of angina, hypertension, renal impairment or acute renal failure.

Also included within the scope of the invention are the synthetic intermediates of the formula :

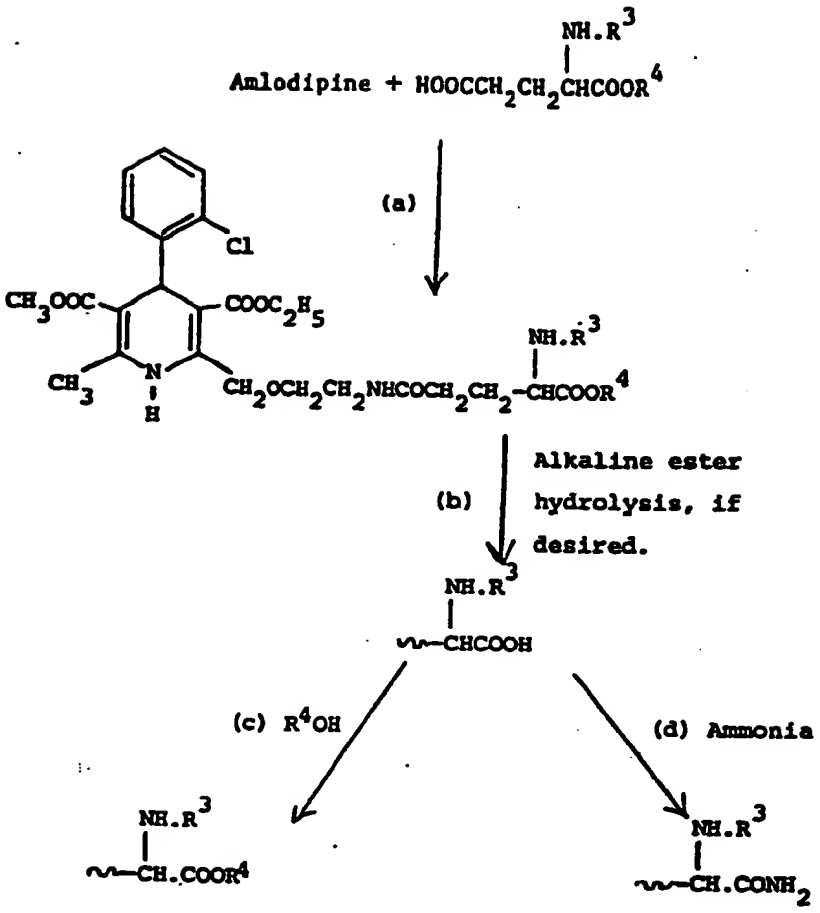


--- (A)

where R is an amino-protecting group, preferably benzyloxycarbonyl or t-butoxycarbonyl, and R^1 is as defined for formula (I).

The compounds of the formula (I) are all preparable by the removal of the amino-protecting group from the corresponding N-protected compounds of the formula (A). As stated above, the preferred protecting groups are benzyloxycarbonyl and t-butoxycarbonyl. These can be removed by conventional methods. For example, the benzyloxycarbonyl group is typically removed by the hydrogenolysis of the N-protected 1,4-dihydropyridine in a suitable solvent, e.g. 10% aqueous ethanol, under an atmosphere of hydrogen at, say, 15-30 p.s.i. (103.4-206.8 kPa) at about room temperature and in the presence of a 5% palladium on carbon catalyst. The t-butoxycarbonyl group is typically removed by treatment with an acid, e.g. by treatment of the N-protected 1,4-dihydropyridine at about room temperature in a suitable organic solvent, e.g. dichloromethane, with gaseous hydrogen chloride.

The N-protected starting materials can be prepared by conventional techniques which are illustrated schematically as follows :



In the above, R^3 is an amino-protecting group and R^4 is C_1-C_6 alkyl, phenyl or benzyl. The phenyl and benzyl groups are optionally substituted as defined for R^2.

The coupling reactions of steps (a) and (c) are typically carried out by forming an "activated" derivative of the acid in situ as will be known to those skilled in the art, typically by reacting the acid with 1-hydroxybenzotriazole, 4-dimethylaminopyridine or N-hydroxysuccinimide in the presence of N,N'-dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide at about room temperature in a suitable organic solvent such as dichloromethane. The "activated" derivative is then reacted with amlodipine in setp (a) or the alcohol in step (c). Since 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide is most readily available as the hydrochloride salt, it is typically used in the process in salt form but in the presence of a base such as triethylamine.

Similarly, the amides are typically formed in step (d) by reacting the acid with, e.g., carbonyldiimidazole so as to form an "activated" derivative of the acid (i.e. an acyl imidazole), followed by reaction of the "activated" derivative with ammonia. These reactions are usually carried out at between 0° and room temperature in an appropriate organic solvent, e.g. tetrahydrofuran, and the ammonia is typically used in gaseous form.

The alkaline hydrolysis of step (b) is preferably carried out by reacting the ester in an organic solvent such as dioxan with aqueous sodium hydroxide at about room temperature.

The N-protected amino-acid starting materials are either commercially available (especially in the S-form) or are preparable by conventional techniques such as those illustrated in the following experimental section.

The pharmaceutically acceptable acid addition salts of the compounds of the formula (I) are those formed from acids which form non-toxic acid addition salts, for example the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or acid phosphate, acetate, citrate, fumarate, gluconate, lactate, maleate, succinate, tartrate, methanesulphonate, benzenesulphonate and p-toluenesulphonate salts.

The compounds of the formula (I) in which R^1 is hydroxy also form metal salts. The alkali metal salts, and especially the sodium and potassium salts, are preferred.

All the salts can be prepared conventionally.

When R^1 is hydroxy, the compounds of the formula (I) may exist in zwitterionic form and such forms are

also within the scope of this invention.

The compounds of the formula (I) have two chiral centres and the invention includes both the resolved and unresolved forms. For synthetic convenience, it is preferred to use amlodipine in its R/S form and the N-protected amino-acid in its S-form.

The effect of the compounds of the formula (I) on coronary blood flow and urinary excretion of sodium in anaesthetised dogs can be measured as follows :

Dogs are anaesthetised and catheters inserted into blood vessels for the measurement of blood pressure, heart rate and coronary blood flow. Urine is collected from catheters inserted into both ureters and the concentration of sodium determined. The animals receive a continuous intravenous infusion of 0.9% sodium chlorid in water at a rate of 10 ml/kg/h. The effect of the test compound is assessed by observing the changes in coronary blood flow and changes in urinary excretion of sodium following intravenous administration of the test compound.

The antihypertensive activity of the compounds can be measured by the following techniques :

The antihypertensive activity of the test compound administered by intravenous injection is determined by measuring the fall in the blood pressure of renally hypertensive conscious dogs. In addition, the compounds can also be administered orally to spontaneously hypertensive rats.

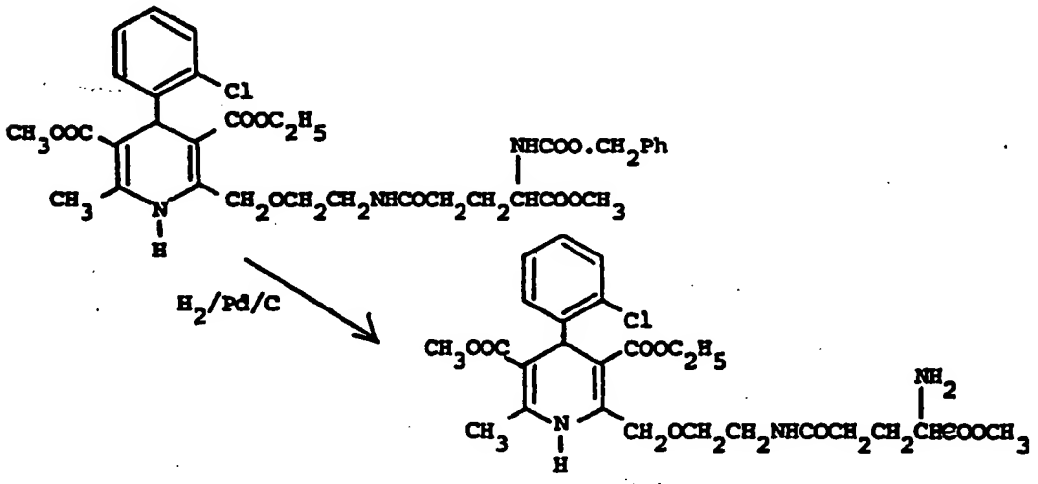
The natriuretic activity of the compounds can be assessed in conscious dogs as follows :

Dogs are fasted for 24 hours before the experiment. Urine is collected from the dogs over three 30 minute time periods to determine the baseline excretion rate of sodium. A dose of 3 mEq/kg sodium chloride (as a 0.9% solution in water) is administered orally and further urine samples are collected for 3 hours. The recovery of the oral sodium load from the urine is calculated as the total recovery in 3 hours minus the baseline sodium excretion. A compound is deemed to have natriuretic activity if its prior administration, for example by intravenous injection, causes a significant increase in urinary sodium excretion over the 3 hour test period.

The following Examples, in which all temperatures are in °C, illustrate the invention :

EXAMPLE 1

2-[2-(-(S)-4-Amino-4-methoxycarbonylbutanamido) ethoxymethyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine



A solution of 2-[2-(-(S)-4-benzyloxycarbonylamino-4-methoxycarbonylbutanamido)ethoxymethyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (0.89 g) in 10% aqueous

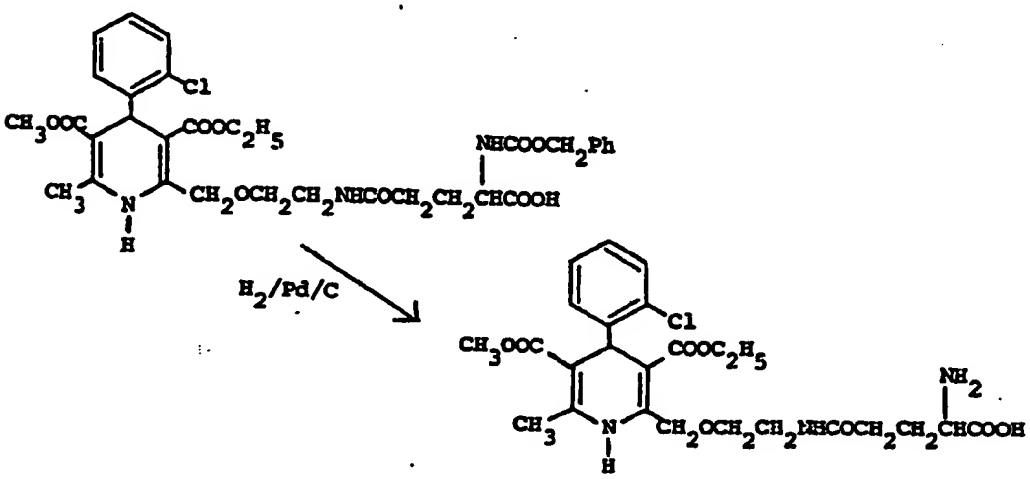
ethanol (22 ml) was stirred for 2 hours under an atmosphere of hydrogen [103.4 kPa (15 p.s.i.)] at room temperature in the presence of 5% palladium on carbon (90 mg). The mixture was filtered and evaporated and the residue purified by chromatography on silica using dichloromethane plus 0 → 4% methanol as the eluant. Appropriate fractions were combined and evaporated to leave the title compound (0.38 g) as an oil.

N.m.r. (300 mHz, $CDCl_3$) : δ = 1.20 (3H, t, 3-$CO_2CH_2\underline{CH_3}$) ; 1.8-2.6 (4H, m, 2 × $\underline{CH_2}$) ; 2.4 (3H, s, 6-$\underline{CH_3}$) ; 3.4-3.8 (10 H, m, 2 × $\underline{CH_2}$, 3-$CO_2\underline{CH_3}$, 5-$CO_2\underline{CH_3}$) ; 4.1 (2H, m, 3-$CO_2\underline{CH_2}CH_3$) ; 4.8 (2H, m, 2-$\underline{CH_2}$-O—) ; 5.4 (1H, s, 4-$\underline{H}$) ; 7.0-7.6 (4H, m, $\underline{ArH}$).

Mass spectra m/e $(M + H)^+$ = 552.

EXAMPLE 2

2-[2-(-(S)-4-Amino-4-carboxybutanamido) ethoxymethyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine



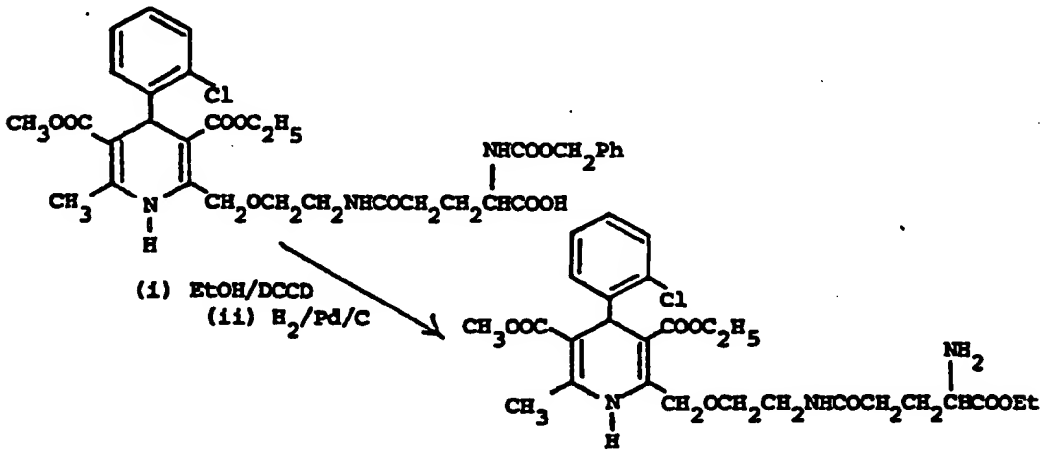
A solution of 2-[2-(-(S)-4-benzyloxycarbonylamino-4-carboxybutanamido)ethoxymethyl]-4-(2-chlorophenyl)-3-ethoxy-carbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (0.97 g) in 10% aqueous ethanol (22 ml) was stirred for 2 hours under an atmosphere of hydrogen [103.4 kPa (15 p.s.i.)] at room temperature in the presence of 5% palladium on carbon (97 mg). The mixture was filtered and evaporated to leave the title compound as an amorphous solid, (0.7 g).

Analysis % :

Found :	C, 54.01 ; H, 6.16 ; N,7.56 ;
$C_{25}H_{32}ClN_3O_8 \cdot H_2O$ requires :	C, 54.07 ; H, 5.87 ; N, 7.62.

EXAMPLE 3

2-[2-(-(S)-4-Amino-4-ethoxycarbonylbutanamido) ethoxymethyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine



A mixture of 2-[2-(-(S)-4-benzyloxycarbonylamino-4-carboxybutanamido)ethoxymethyl]-4-(2-chlorophenyl)-3-ethoxy-carbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (1.0 g), ethanol (0.27 g), N,N'-dicyclohexylcarbodiimide ("DCCD") (0.34 g) and 4-dimethylaminopyridine (50 mg) was stirred in dichloromethane (10 ml) at room temperature for 18 hours. The resulting N,N'-dicyclohexylurea was then removed by filtration and the filtrate evaporated. The residue was purified by chromatography on silica using dichloromethane plus 0 → 2% methanol as the eluant. Appropriate fractions were combined and evaporated to give 2-[2-(-(S)-4-benzyloxycarbonylamino-4-ethoxycarbonylbutanamido) ethoxymethyl]-4-(2-chlorophenyl-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (0.85 g) as an essentially pure oil.

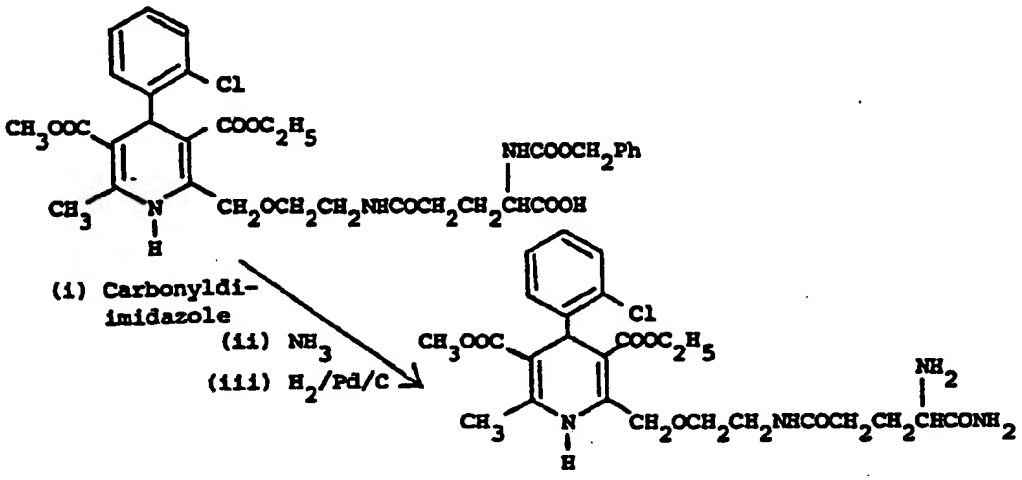
The above oil in 10% aqueous ethanol (22 ml) containing 5% Pd on C(0.085 g) was hydrogenated and purified as described in Example 1 above to give the title compound (0.55 g) as an oil.

N.m.r. (300 mHz, $CDCl_3$) : δ = 1.20 (3H, t, 3-$CO_2CH_2\underline{CH_3}$) ; 1.25 (3H, t, $CO_2CH_2\underline{CH_3}$) ; 1.8-2.6 (4H, m, 2 × $\underline{CH_2}$); 2.4 (3H, s, 6-$\underline{CH_3}$) ; 3.4-3.8 (7H, m, 2 × $\underline{CH_2}$, 5-$CO_2\underline{CH_3}$) ; 4.1 (2H, m, 3-$CO_2\underline{CH_2}CH_3$) ; 4.2 (2H, q, $CO_2\underline{CH_2}CH_3$); 4.7 (2H, m, 2-$\underline{CH_2}O$) ; 5.4 (1H, s, 4-$\underline{H}$) ; 7.0-7.6 (4H, m, $\underline{ArH}$).

Mass spectra : m/e $(M + H)^+$ = 566.

EXAMPLE 4

2-[2-(-(S)-4-Amino-4-carbamoylbutanamido) ethoxymethyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine



Carbonyldiimidazole (0.36 g) was added to an ice cold solution of 2-[2-(-(S)-4-benzyloxycarbonylamino-4-carboxy-butanamido)ethoxymethyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (1.0 g) in tetrahydrofuran (20 ml). After allowing the reaction mixture to reach room temperature, the mixture was stirred for 2 hours and then treated with gaseous ammonia for ½ hour. The mixture was then evaporated and the residue partitioned between 10% aqueous sodium carbonate solution and ethyl acetate. The aqueous layer was extracted with two further portions of ethyl acetate. The organic extracts were combined, washed with brine, dried over magnesium sulphate and evaporated. The residue was purified by chromatography on silica, eluting with dichloromethane plus 0 → 5% methanol. Appropriate fractions were combined and evaporated to give 2-[2-(-(S)-4-benzyloxycarbonylamino-4-carbamoylbutanamido)-ethoxymethyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (0.84 g) as an essentially pure oil.

The above oil in 10% aqueous ethanol (22 ml) containing 5% Pd on C (0.085 g) was hydrogenated as described in Example 1. Purification was by chromatography on silica using dichloromethane containing 1% ammonia and 2 → 10% methanol as the eluant. The title compound (0.52 g) was obtained as an oil.

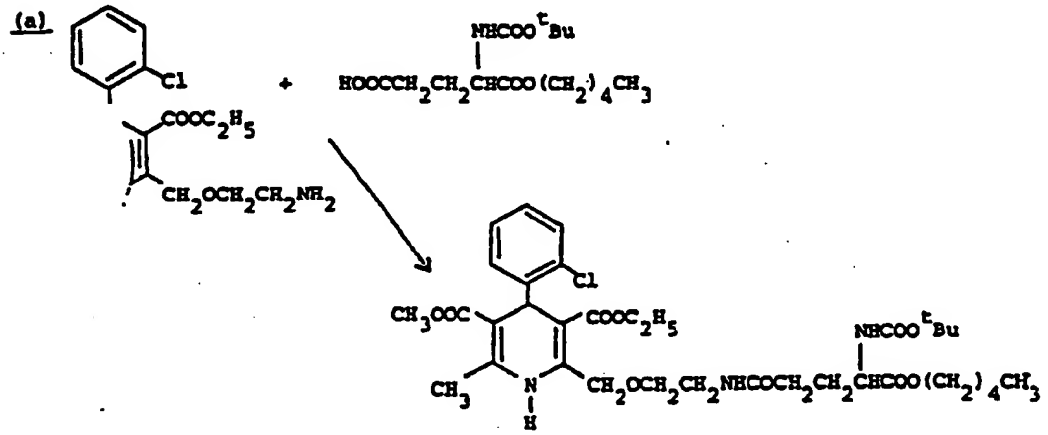
N.m.r. (300 mHz, $CDCl_3$) : δ = 1.2 (3H, t, 3-$CO_2CH_2\underline{CH_3}$) ; 1.6-2.6 (4H, m, 2 × $\underline{CH_2}$) ; 2.4 (3H, s, 6-$\underline{CH_3}$) ; 3.4-3.8 (7H, m, 2 × $\underline{CH_2}$, 5-$CO_2\underline{CH_3}$) ; 4.1 (2H, m, 3-$CO_2\underline{CH_2}CH_3$) ; 4.7 (2H, m, 2-$\underline{CH_2}O$) ; 5.3 (1H, s, 4-$\underline{H}$) ; 5.5 (1H, br s, $\underline{NH}$) ; 6.8 (1H, br s, $\underline{NH}$) ; 7.0-7.5 (4H, m, $\underline{ArH}$).

Mass spectra : m/e $(M + H)^+$ = 537.

EXAMPLE 5

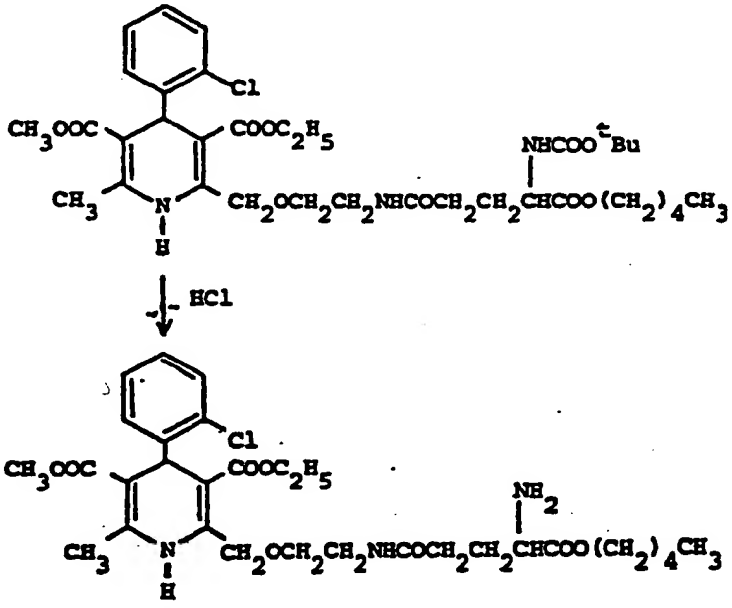
2-[2-(-(S)-4-Amino-4-n-pentoxycarbonylbutanamido) ethoxymethyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-m thyl-1,4-dihydropyridine

(a)



A mixture of 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine ("amlodipine") (3.93 g), (S)-4-(t-butoxycarbonylamino)-4-n-pentoxycarbonylbutanoic acid (3.36 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.03 g), 1-hydroxybenzotriazole (1.43 g) and triethylamine (1.07 g) was stirred in dichloromethane (60 ml) at room temperature for 18 hours. After evaporation the residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with three further portions of ethyl acetate. The organic extracts were combined, washed with brine, dried over magnesium sulphate and evaporated. The residue was purified by chromatography on silica eluting with dichloromethane containing gradually increasing amounts (0 → 2%) of methanol. Appropriate fractions were combined and evaporated to give 2-[2-(-(S)-4-t-butoxycarbonylamino-4-n-pentoxycarbonylbutanamido) ethoxymethyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (4.7 g) as an essentially pure oil.

(b)



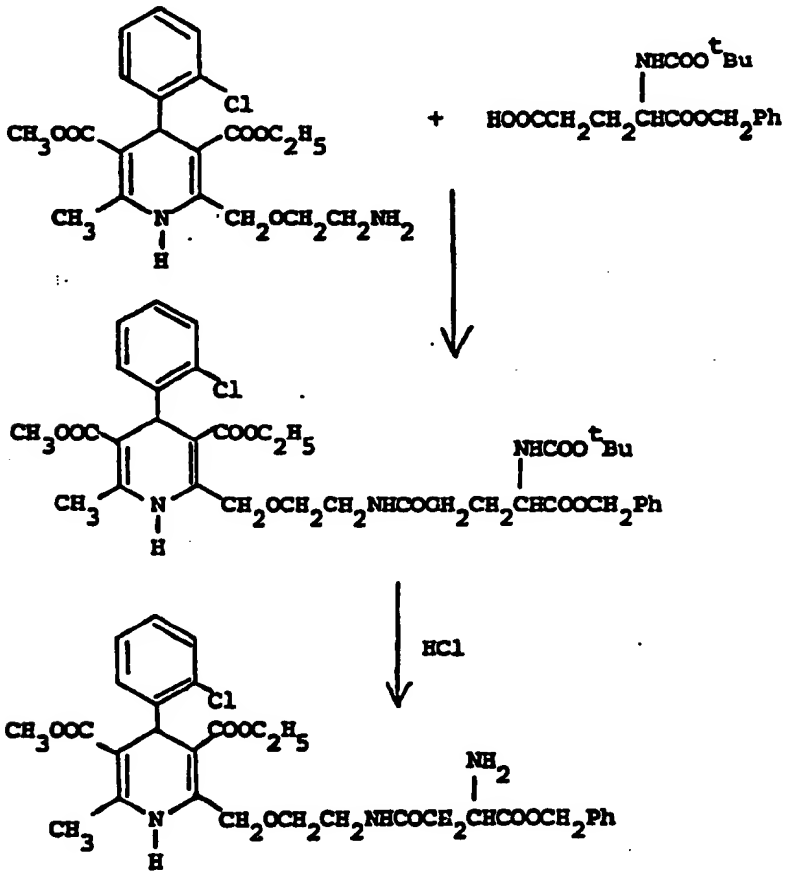
The oil from part (a) above (2.3 g) in dichloromethane (75 ml.) was treated at room temperature with gaseous hydrogen chlorid for 2 hours. After air-induced removal of excess hydrogen chloride, the mixture was evaporated and the residue partition d betw en ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic layer was washed with brine, dried over magnesium sulphate and evaporated. The residue was purified by chromatography on silica using dichloromethane containing 0→4% methanol as the eluant. Appropriate fractions were combined and evaporated to give the title compound (0.5 g) as an oil.

N.m.r. (300 mHz, $CDCl_3$) : δ = 0.9 (3H, t, $—O(CH_2)_4\underline{CH_3}$) ; 1.2 (3H, t, 3-$CO_2CH_2\underline{CH_3}$) ; 1.3 (4H, m, $—CO_2CH_2\underline{CH_2CH_2CH_2CH_3}$) ; 1.5-2.5 (6H, m, 3 × $\underline{CH_2}$) ; 2.4 (3H, s, 6-$\underline{CH_3}$) ; 3.2-3.7 (7H, m, 2-$CH_2O\underline{CH_2CH_2}$, 5-$CO_2\underline{CH_3}$) ; 4.1 (4H, m, $—CO_2\underline{CH_2}C_4H_9$, 3-$CO_2\underline{CH_2}CH_3$) ; 4.7 (2H, m, 2-$\underline{CH_2}O$) ; 5.4 (1H, s, 4-$\underline{H}$) ; 7.0-7.6 (4H, m, ArH).

Mass spectra : m/e $(M + H)^+$ = 608.

EXAMPLE 6

2-[2-(-(S)-4-Amino-4-benzyloxycarbonylbutanamido) ethoxymethyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine



The title compound (0.29 g) was prepared as an oil by the reaction of amlodipine (1.1 g), (S)-4-benzyloxycarbonyl-4-t-butoxycarbonylaminobutanoic acid (1.0 g) (commercially available), 1-(3-dimethylaminopropyl)-3-ethylcarbonlimide hydrochloride (0.57 g), 1-hydroxybenzotriazole (0.40 g) and triethylamine (0.30 g) according to method of part (a) of Example 5 followed by treatment of the resulting intermediate in dichloromethane with gaseous hydrogen chloride according to the method of part (b).

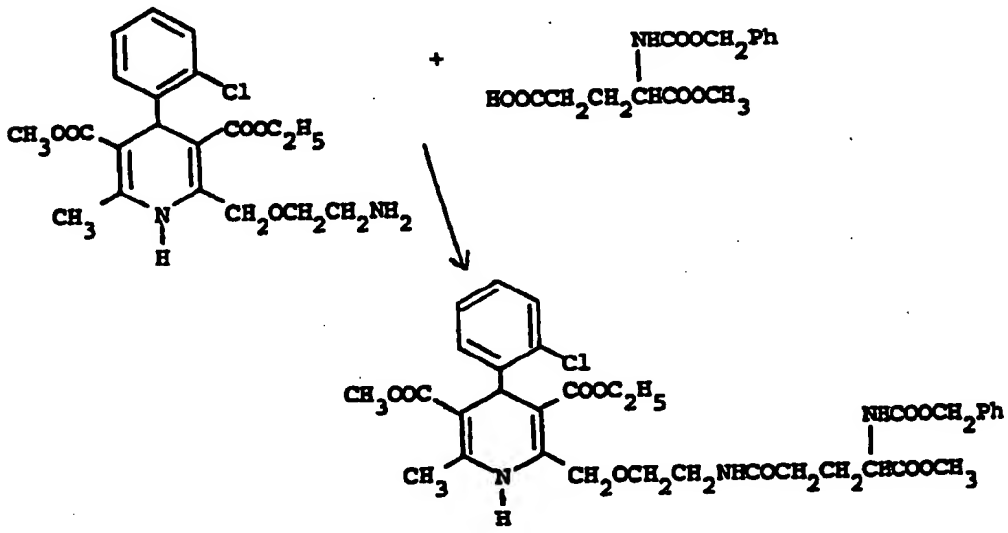
N.m.r. (300 mHz, $CDCl_3$) : δ = 1.2 (3H, t, 3-$CO_2CH_2\underline{CH_3}$) ; 1.6-2.6 (4H, m, 2 × $\underline{CH_2}$) ; 2.4 (3H, s, 6-$\underline{CH_3}$) ; 3.3-3.8 (7H, m, 2-$CH_2O\underline{CH_2CH_2}$, 5-$CO_2\underline{CH_3}$) ; 4.0 (2H, q, 3-$CO_2\underline{CH_2}CH_3$) ; 4.7 (2H, m, 2-$\underline{CH_2}O$) ; 5.1 (2H, s, $\underline{CH_2}Ph$) ; 5.4 (1H, s, 4-$\underline{H}$) ; 7.0-7.4 (9H, m, ArH).

Mass spectra m/e $(M + H)^+$ = 628.

The following Preparations, in which all temperatures are in °C, illustrate the preparation of certain of the starting materials used in the previous Examples :

Preparation 1

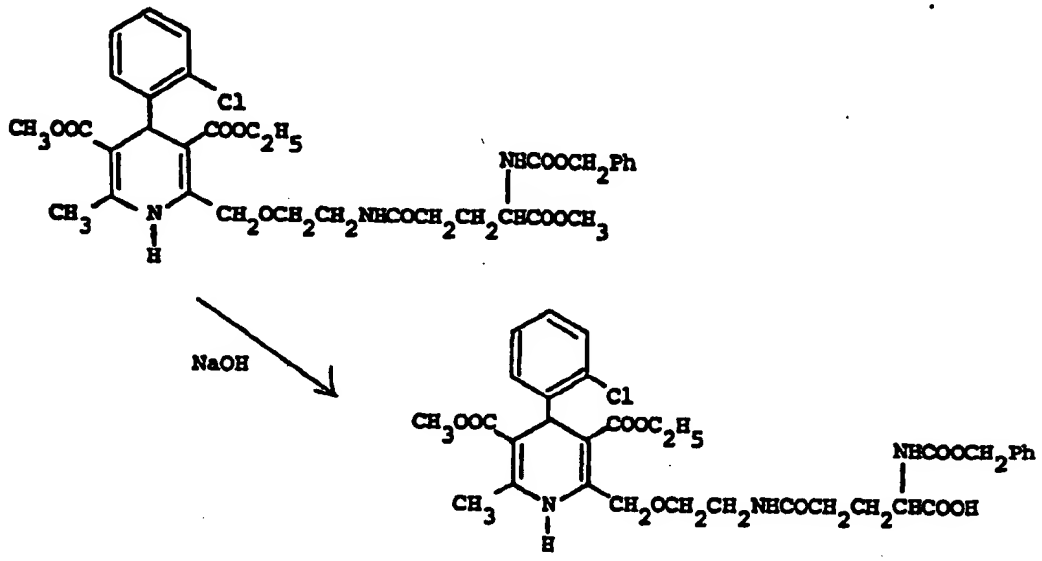
2-[2-(-(S)-4-Benzyloxycarbonylamino-4-methoxycarbonylbutanamido) ethoxymethyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine



A mixture of 2-[2-aminoethoxymethyl]-4-(2-chlorophenyl-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (1.61 g), ("amlodipine"), (S)-4-benzyloxycarbonylamino-4-methoxycarbonylbutanoic acid (1.28 g) [see G.H.L. Nefkens and J. F. Nivard, Rec. Trav. Chim. Pays Bas, 199, 83, 1964], 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.83 g), 1-hydroxybenzotriazole (0.59 g) and triethylamine (0.44 g) in dichloromethane (25 ml) were reacted together as described in Example 5 part (a) to give the title compound (2.0 g) as an essentially pure solid foam which was used directly in Example 1 and Preparation 2 without further purification.

Preparation 2

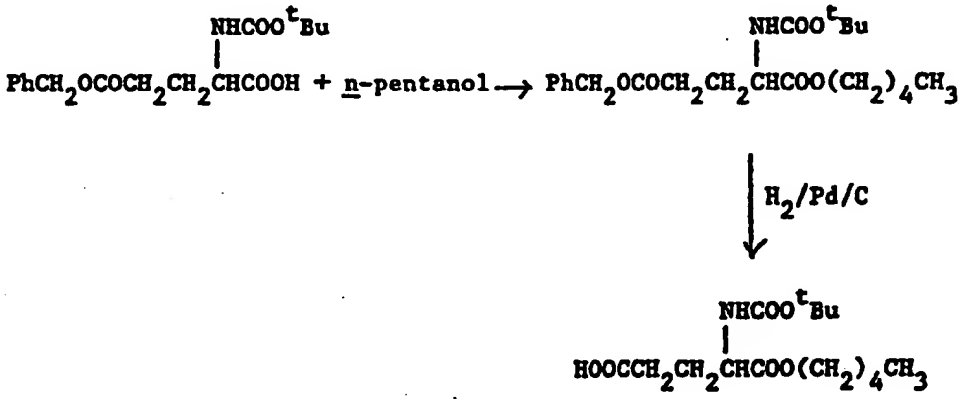
2-[2-(-(S)-4-Benzyloxycarbonylamino-4-carboxybutanamido) ethoxymethyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine



1M Aqueous sodium hydroxide (8.75 ml) was added to a solution of the product of Preparation 1 above (2.0 g) in dioxan (18 ml). After 2 hours at room temperature the mixture was evaporated and the residue partitioned between ethyl acetate and 1M hydrochloric acid. The organic layer was separated, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography using dichloromethane containing ammonia (1%) and increasing amounts of methanol (10 → 15%) as the eluant. Appropriate fractions were combined and evaporated to give the title compound (0.97 g) as a foam which was used directly in Examples 2, 3 and 4 without further purification.

Preparation 3

(S)-4-t-Butoxycarbonylamino-4-pentoxycarbonylbutanoic acid



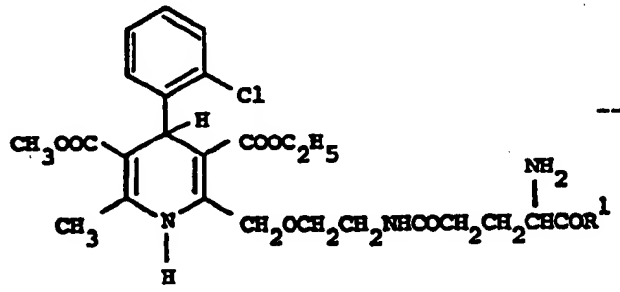
A mixture of (S)-benzyl 4-t-butoxycarbonylamino-4-carboxybutanoate (5 g) (commercially available), N,N'-dicyclohexylcarbodiimide (3.35 g), 4-dimethlaminopyridine (150 mg) and n-pentanol (5.2 g) was stirred in dichloromethane (30 ml) for 18 hours. The resulting N,N'-dicyclohexylurea was removed by filtration and the filtrate evaporated. The residue was dissolved in hexane, filtered and the filtrate evaporated to give (S)-benzyl 4-t-butoxycarbonylamino-4-pentoxycarbonylbutanoate (6 g) as an essentially pure oil.

This oil (4.1 g) in 10% aqueous ethanol (90 ml) containing 5% Pd on C (0.41 g) was hydrogenated as described in Example 1 above to give the title compound (3.36 g) as an essentially pure oil which was used directly in Example 5.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound of the formula :



--- (I)

or a pharmaceutically acceptable salt thereof, wherein R^1 is —OR^2 or —NH_2 in which R^2 is H, C_1-C_8 alkyl, phenyl or benzyl, the phenyl and benzyl groups being optionally substituted on the aromatic ring by one or two substituents each selected from C_1-C_4 alkyl, C_1-C_4 alkoxy and halo.

2. A compound as claimed in claim 1 wherein R^2 is H, C_1-C_8 alkyl, unsubstituted phenyl or unsubstituted benzyl.

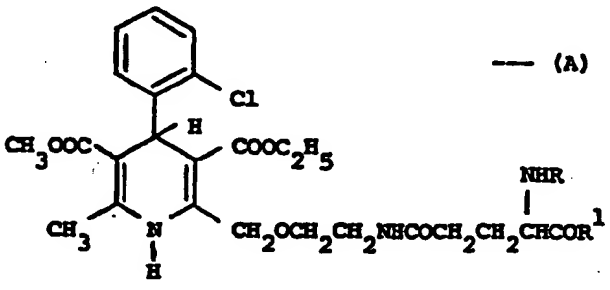
3. A compound as claimed in claim 2 wherein R_1 is —OH.

4. A pharmaceutical composition comprising a compound of the formula (I) as claimed in any one of the preceding claims, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

5. A compound of the formula (I) as claimed in any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, for use as a medicament.

6. The use of a compound of the formula (I) as claimed in any one of claims 1 to 3, or of a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for treating hypertension, angina, renal impairment or acute renal failure.

7. A compound of the formula :



--- (A)

wherein R is an amino-protecting group, and R^1 is as defined in any one of claims 1 to 3.

8. A compound as claimed in claim 7, wherein R is benzyloxycarbonyl or t-butoxycarbonyl.

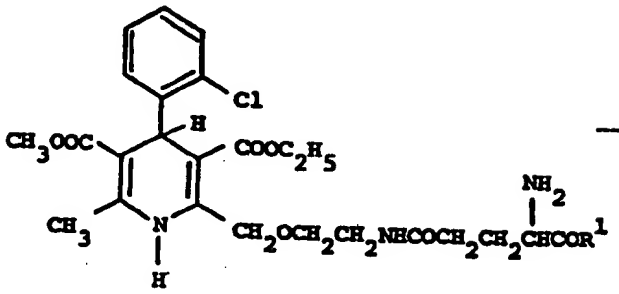
9. A process for preparing a compound of the formula (I) as claimed in any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, characterised by removing th amino-protecting group R from a compound of the formula (A) as claimed in claim 7.

10. A process as claimed in claim 9, wherein the amino-protecting group is either (a) benzyloxycarbonyl, which is removed by catalytic hydrogenation or (b) t-butoxycarbonyl, which is removed by treatment with an

acid.

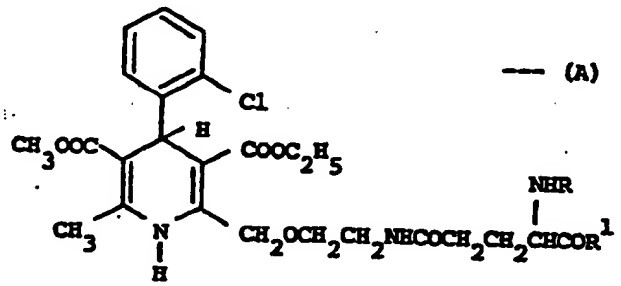
Claims for the following C ntra ting State : GR

1. A process for preparing a compound of the formula :



— (I)

or a pharmaceutically acceptable salt thereof, wherein R^1 is —OR^2 or —NH_2 in which R^2 is H, C_1-C_8 alkyl, phenyl or benzyl, the phenyl and benzyl groups being optionally substituted on the aromatic ring by one or two substituents each selected from C_1-C_4 alkyl, C_1-C_4 alkoxy and halo, characterised by removing the amino-protecting group R from a compound of the formula :



— (A)

wherein R is an amino-protecting group and R^1 is as defined for formula (I) ; said process being followed by, optionally, conversion of the product of the formula (I) into a pharmaceutically acceptable salt.

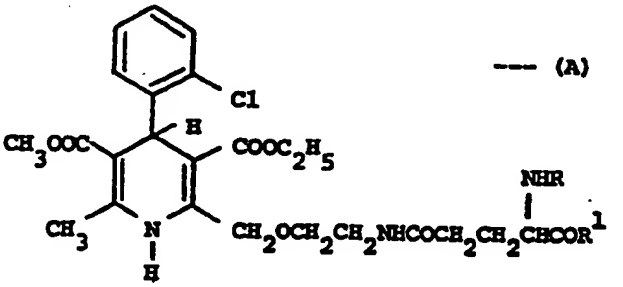
2. A process according to claim 1, characterised in that R^1 is —OH.

3. A process according to claim 1 or 2, characterised in that R is benzyloxycarbonyl or t-butoxycarbonyl.

4. A process according to claim 3, characterised in that the benzyloxycarbonyl group is removed by catalytic hydrogenation, and the t-butoxycarbonyl group by treatment with an acid.

5. A process as claimed in claim 4, characterised in that the acid is gaseous hydrogen chloride.

6. A compound of the formula :



— (A)

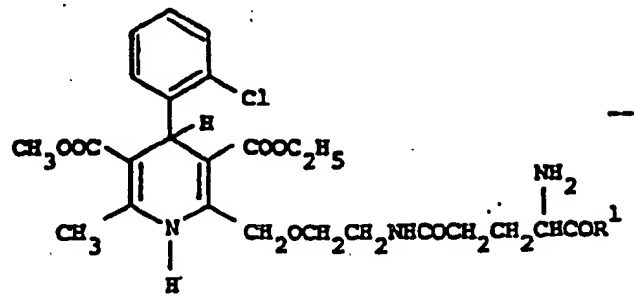
wherein R is an amino-protecting group and R^1 is as defined in claim 1.

7. A compound as claimed in claim 6 wherein R^1 is —OH.

8. A compound as claimed in claim 6 or 7 wherein R is benzyloxycarbonyl or t-butoxycarbonyl.

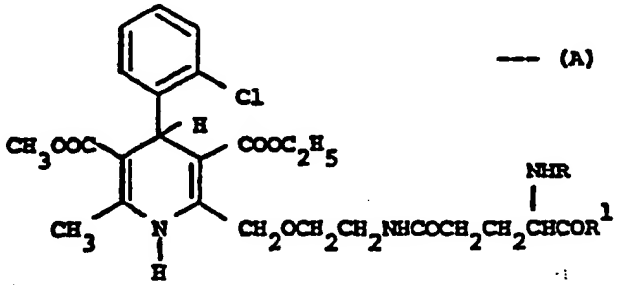
Claims for the following Contracting State : ES

1. A process for preparing a compound of the formula :



--- (I)

or a pharmaceutically acceptable salt thereof, wherein R^1 is —OR^2 or —NH_2 in which R^2 is H, C_1-C_6 alkyl, phenyl or benzyl, the phenyl and benzyl groups being optionally substituted on the aromatic ring by one or two substituents each selected from C_1-C_4 alkyl, C_1-C_4 alkoxy and halo, characterised by removing the amino-protecting group R from a compound of the formula :



--- (A)

wherein R is an amino-protecting group and R^1 is as defined for formula (I) ; said process being followed by, optionally, conversion of the product of the formula (I) into a pharmaceutically acceptable salt.

2. A process according to claim 1, characterised in that R^1 is —OH.

3. A process according to claim 1 or 2, characterised in that R is benzyloxycarbonyl or t-butoxycarbonyl.

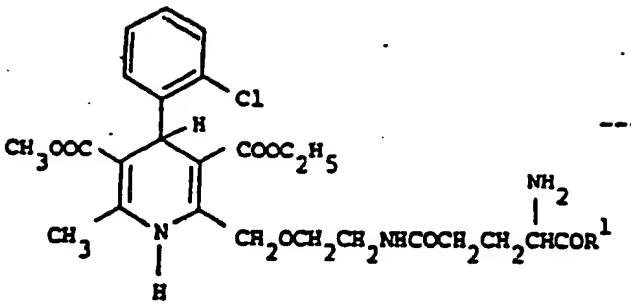
4. A process according to claim 3, characterised in that the benzyloxycarbonyl group is removed by catalytic hydrogenation, and the t-butoxycarbonyl group by treatment with an acid.

5. A process as claimed in claim 4, characterised in that the acid is gaseous hydrogen chloride.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verbindung der Formel :



--- (I)

oder ein pharmazeutisch annehmbares Salz davon, worin R^1 —OR^2 oder —NH_2 ist, worin R^2 H, eine C_1-C_6-Alkyl-, Phenyl- oder Benzylgruppe ist, wobei die Phenyl- und Benzylgruppen gegebenenfalls am aromatischen Ring mit einem oder zwei Substituenten substituiert sind, die jeweils ausgewählt sind aus einer C_1-C_4-Alkylgruppe, C_1-C_4-Alkoxygruppe und Halogen.

2. Verbindung nach Anspruch 1, worin R^2 H, eine C_1-C_6-Alkylgruppe, unsubstituierte Phenylgruppe oder unsubstituierte Benzylgruppe ist.

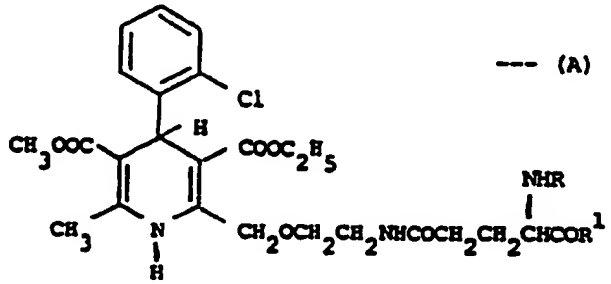
3. Verbindung nach Anspruch 2, worin R^1 —OH ist.

4. Pharmazeutische Zusammensetzung, enthaltend eine Verbindung der Formel (I) wie in einem der vorhergehenden Ansprüche oder ein pharmazeutisch annehmbares Salz davon und ein pharmazeutisch annehmbares Verdünnungsmittel oder Trägermittel.

5. Verbindung der Formel (I) nach einem der Ansprüche 1 bis 3 oder ein pharmazeutisch annehmbares Salz davon zur Verwendung als Arzneimittel.

6. Verwendung einer Verbindung der Formel (I) nach einem der Ansprüche 1 bis 3 oder eines pharmazeutisch annehmbaren Salzes davon zur Verwendung zur Herstellung eines Arzneimittels zur Behandlung von Bluthochdruck, Angina, Nierenschäden oder akutem Nierenversagen.

7. Verbindung der Formel :



--- (A)

worin R eine Aminoschutzgruppe ist und R^1 wie in einem der Ansprüche 1 bis 3 definiert ist.

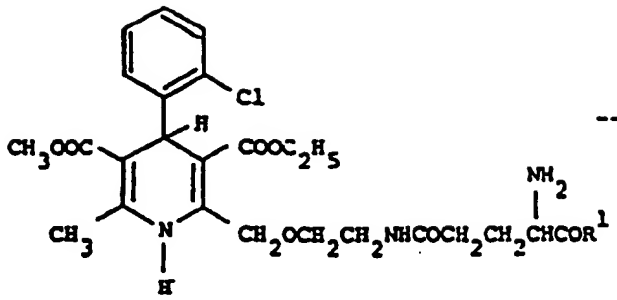
8. Verbindung nach Anspruch 7, worin R eine Benzyloxycarbonyl- oder t-Butoxycarbonylgruppe ist.

9. Verfahren zur Herstellung einer Verbindung der Formel (I) nach einem der Ansprüche 1 bis 3 oder eines pharmazeutisch annehmbaren Salzes davon, dadurch gekennzeichnet, daß die Aminoschutzgruppe R von einer Verbindung der Formel (A) gemäß Anspruch 7 entfernt wird.

10. Verfahren nach Anspruch 9, worin die Aminoschutzgruppe entweder (a) eine Benzyloxycarbonylgruppe ist, die durch katalytische Hydrierung entfernt wird oder (b) eine t-Butoxycarbonylgruppe ist, die durch Behandlung mit einer Säure entfernt wird.

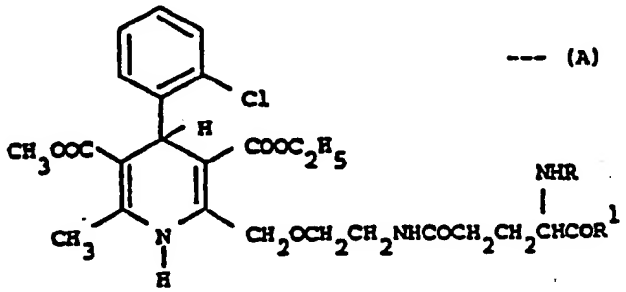
Patentanspüche für folgenden Vertragsstaat GR

1. Verfahren zur Herstellung einer Verbindung der Formel :



--- (I)

oder eines pharmazeutisch annehmbaren Salzes davon, worin R^1 —OR^2 oder —NH_2 ist, wobei R^2 H, eine C_1-C_6-Alkyl-, Phenyl- oder Benzylgruppe ist, wobei die Phenyl- und Benzylgruppen gegebenenfalls am aromatischen Ring mit einem oder zwei Substituenten substituiert sind, die jeweils ausgewählt sind aus einer C_1-C_4-Alkylgruppe, C_1-C_4-Alkoxygruppe und Halogen, dadurch gekennzeichnet, daß die Aminoschutzgruppe R von einer Verbindung der Formel :



--- (A)

entfernt wird, worin R eine Aminoschutzgruppe ist und R^1 wie für Formel (I) definiert ist ; wobei sich an das Verfahren gegebenenfalls die Umwandlung des Produktes der Formel (I) in ein pharmazeutisch annehmbares Salz anschließt.

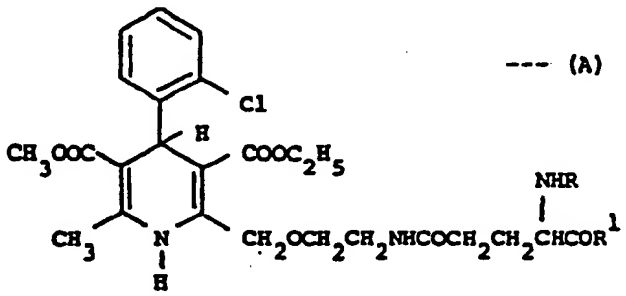
2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß R^1 —OH ist.

3. Verfahren nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß R eine Benzyloxycarbonyl- oder t-Butoxycarbonylgruppe ist.

4. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß die Benzyloxycarbonylgruppe durch katalytische Hydrierung entfernt wird und die t-Butoxycarbonylgruppe durch Behandlung mit einer Säure entfernt wird.

5. Verfahren nach Anspruch 4, dadurch gekennzeichnet, daß die Säure gasförmiger Chlorwasserstoff ist.

6. Verbindung der Formel :



--- (A)

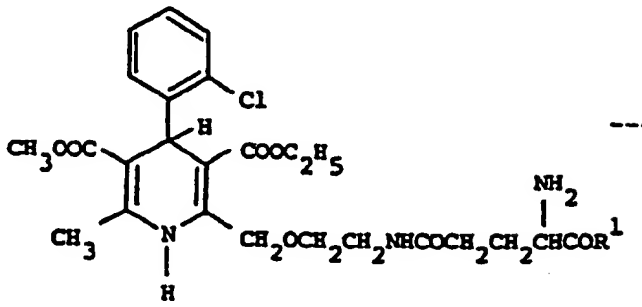
worin R eine Aminoschutzgruppe und R^1 wie in Anspruch 1 definiert ist.

7. Verbindung nach Anspruch 6, worin R^1 —OH ist.

8. Verbindung nach Anspruch 6 oder 7, worin R eine Benzyloxycarbonyl- oder t-Butoxycarbonylgruppe ist.

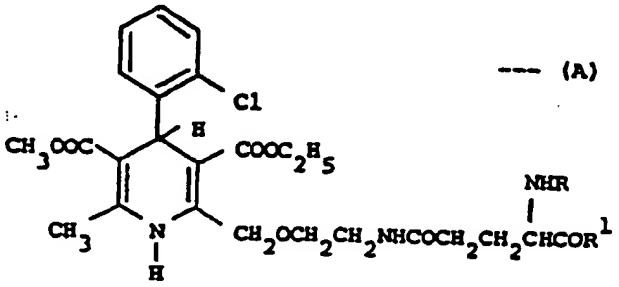
Patentanspruch für folgenden Vertragstaat : ES

1. Verfahren zur Herstellung einer Verbindung der Formel :



--- (I)

oder eines pharmazeutisch annehmbaren Salzes davon, worin R^1 —OR^2 oder —NH_2 ist, worin R^2 H, eine C_1-C_6-Alkyl-, Phenyl- oder Benzylgruppe ist, wobei die Phenyl- und Benzylgruppen gegebenenfalls am aromatischen Ring mit einem oder zwei Substituenten substituiert sind, die jeweils ausgewählt sind aus einer C_1-C_4-Alkylgruppe, C_1-C_4-Alkoxygruppe und Halogen, dadurch gekennzeichnet, daß die Aminoschutzgruppe R von einer Verbindung der Formel :



--- (A)

entfernt wird, worin R eine Aminoschutzgruppe und R^1 wie für Formel (I) definiert ist ; wobei sich an das Verfahren gegebenenfalls die Umwandlung des Produktes der Formel (I) in ein pharmazeutisch annehmbares Salz anschließt.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß R^1 —OH ist.

3. Verfahren nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß R eine Benzyloxycarbonyl- oder t-Butoxycarbonylgruppe ist.

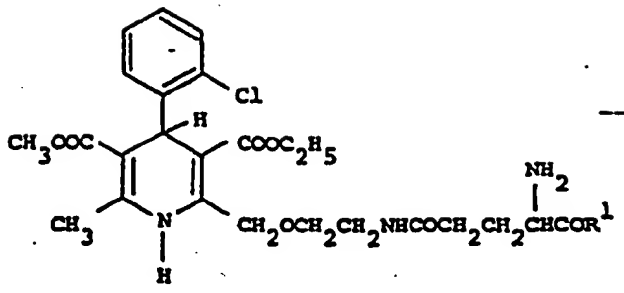
4. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß die Benzyloxycarbonylgruppe durch katalytische Hydrierung entfernt wird und daß die t-Butyloxycarbonylgruppe durch Behandlung mit Säure entfernt wird.

5. Verfahren nach Aspruch 4, dadurch gekennzeichnet, daß die Säure gasförmiger Chlorwasserstoff ist.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composé de formule :



--- (I)

ou sel pharmaceutiquement acceptable de ce composé, dans laquelle R^1 représente —OR^2 ou —NH_2 où R^2 représente H, un groupe alkyle en C_1-C_6, phényle ou benzyle, les groupes phényle et benzyle étant éventuellement substitués sur le noyau aromatique par un ou deux substituants dont chacun est choisi parmi les radicaux alkyle en C_1-C_4, alcoxy en C_1-C_4 et halogéno.

2. Composé selon la revendication 1, dans lequel R^2 représente H, un groupe alkyle en C_1-C_6, phényle non-substitué ou benzyle non-substitué.

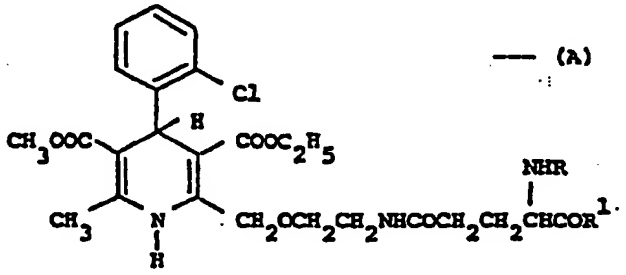
3. Composé selon la revendication 2, dans lequel R^1 représente —OH.

4. Composition pharmaceutique comprenant un composé de formule (I) selon l'une quelconque des revendications précédentes, ou un sel pharmaceutiquement acceptable de ce composé, et un diluant ou véhicule pharmaceutiquement acceptable.

5. Composé de formule (I) selon l'une quelconque des revendications 1 à 3, ou sel pharmaceutiquement acceptable de ce composé, en vue de son utilisation comme médicament.

6. Utilisation d'un composé de formule (I) selon l'une quelconque des revendications 1 à 3, ou d'un sel pharmaceutiquement acceptable de ce composé, pour la fabrication d'un médicament pour le traitement de l'hypertension, de l'angine de poitrine, de troubles rénaux ou de défaillance rénale aiguë.

7. Composé de formule :



--- (A)

dans laquelle R est un groupe amino-protecteur et R^1 est tel que défini dans l'une quelconque des revendications 1 à 3.

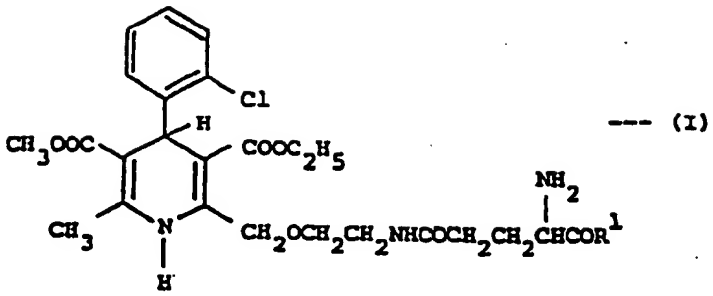
8. Composé selon la revendication 7, dans laquelle R est un groupe benzyloxycarbonyle ou t-butoxycarbonyle.

9. Procédé de préparation d'un composé de formule (I) selon l'une quelconque des revendications 1 à 3, ou d'un sel pharmaceutiquement acceptable de ce composé, caractérisé en ce qu'il consiste à enlever le groupe amino-protecteur R d'un composé de formule (A) selon la revendication 7.

10. Procédé selon la revendication 9, dans lequel le groupe amino-protecteur est soit (a) un groupe benzyloxycarbonyle qui est éliminé par hydrogénation catalytique, soit (b) un groupe t-butoxycarbonyle qui est éliminé par un traitement à l'acide.

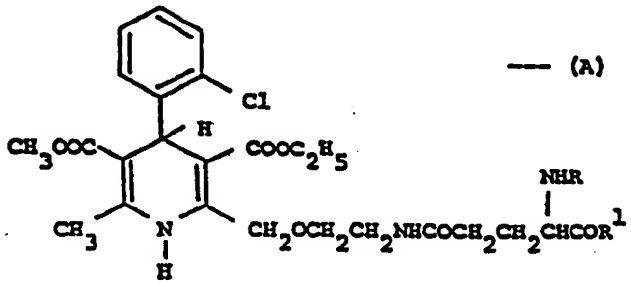
Revendications pour l'Etat contractant suivant : GR

1. Procédé de préparation d'un composé de formule :



--- (I)

ou d'un sel pharmaceutiquement acceptable de ce composé, dans laquelle R^1 représente —OR^2 ou —NH_2, où R^2 représente H, un groupe alkyle en C_1-C_6, phényle ou benzyle, les groupes phényle et benzyle étant éventuellement substitués sur le noyau aromatique par un ou deux substituants dont chacun est choisi parmi les radicaux alkyle en C_1-C_4, alcoxy en C_1-C_4 et halogéno, caractérisé en ce qu'il consiste à enlever le groupe amino-protecteur R d'un composé de formule :



--- (A)

dans laquelle R est un groupe amino-protecteur et R^1 est tel que défini à propos de la formule (I) ; ledit procédé étant suivi, le cas échéant, par la transformation du produit de formule (I) en un sel pharmaceutiquement acceptable.

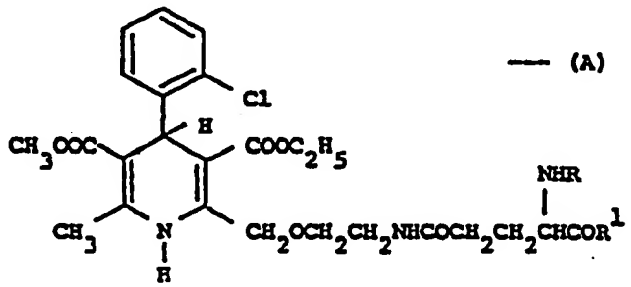
2. Procédé selon la revendication 1, caractérisé en ce que R^1 représente —OH.

3. Procédé selon la revendication 1 ou 2, caractérisé en ce que R est un groupe benzyloxycarbonyle ou t-butoxycarbonyle.

4. Procédé selon la revendication 3, caractérisé en ce que le groupe benzyloxycarbonyle est éliminé par hydrogénation catalytique, et en ce que le groupe t-butoxycarbonyle est éliminé par traitement à l'acide.

5. Procédé selon la revendication 4, caractérisé en ce que l'acide est le chlorure d'hydrogène gazeux.

6. Composé de formule :



--- (A)

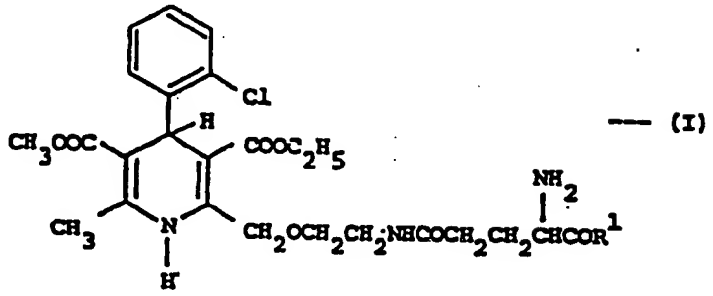
dans laquelle R est un groupe amino-protecteur et R^1 est tel que défini dans la revendication 1.

7. Composé selon la revendication 6, dans lequel R^1 représente —OH.

8. Composé selon la revendication 6 ou 7, dans lequel R est un groupe benzyloxycarbonyle ou t-butoxycarbonyle.

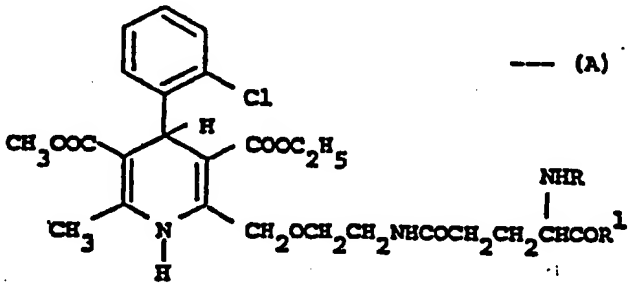
Revendications pour l'Etat contractant suivant : ES

1. Procédé de préparation d'un composé de formule :



— (I)

ou d'un sel pharmaceutiquement acceptable de ce composé, dans laquelle R^1 représente —OR^2 ou —NH_2, où R^2 représente H, un groupe alkyle en C_1-C_6, phényle ou benzyle, les groupes phényle et benzyle étant éventuellement substitués sur le noyau aromatique par un ou deux substituants dont chacun est choisi parmi les radicaux alkyle en C_1-C_4, alcoxy en C_1-C_4 et halogéno, caractérisé en ce qu'il consiste à enlever le groupe amino-protecteur R d'un composé de formule :



— (A)

dans laquelle R est un groupe amino-protecteur et R^1 est tel que défini à propos de la formule (I) ; ledit procédé étant suivi, le cas échéant, par la transformation du produit de formule (I) en un sel pharmaceutiquement acceptable.

2. Procédé selon la revendication 1, caractérisé en ce que R^1 représente —OH.

3. Procédé selon la revendication 1 ou 2, caractérisé en ce que R est un groupe benzyloxycarbonyle ou t-butoxycarbonyle.

4. Procédé selon la revendication 3, caractérisé en ce que le groupe benzyloxycarbonyle est éliminé par hydrogénation catalytique, et en ce que le groupe t-butoxycarbonyle est éliminé par traitement à l'acide.

5. Procédé selon la revendication 4, caractérisé en ce que l'acide est le chlorure d'hydrogène gazeux.